

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:
- 5 (a) the nucleotide sequence as set forth in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 7, or SEQ ID NO: 11;
- (b) the nucleotide sequence of the DNA insert in any of ATCC Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964;
- 10 (c) a nucleotide sequence encoding the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;
- (d) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) - (c); and
- (e) a nucleotide sequence complementary to any of (a) - (c).
- 15 2. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:
- (a) a nucleotide sequence encoding a polypeptide which is at least about 70 percent identical to the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, wherein the encoded
- 20 polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;
- (b) a nucleotide sequence encoding an allelic variant or splice variant of the nucleotide sequence as set forth in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 7, or SEQ ID NO: 11, the nucleotide sequence of the DNA insert in
- 25 any of ATCC Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964, or (a);
- (c) a region of the nucleotide sequence of any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 7, or SEQ ID NO: 11, the DNA insert in any of ATCC Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964, (a), or (b) encoding a polypeptide fragment of at least about 25 amino acid residues, wherein the
- 30 polypeptide fragment has an activity of the encoded polypeptide as set forth in

any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, or is antigenic;

(d) a region of the nucleotide sequence of any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 7, or SEQ ID NO: 11, the DNA insert in any of ATCC
5 Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964, or any of (a) - (c) comprising a fragment of at least about 16 nucleotides;

(e) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) - (d); and

(f) a nucleotide sequence complementary to any of (a) - (d).

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3' An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least
15 one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(b) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least
20 one amino acid insertion, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(c) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least
25 one amino acid deletion, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(d) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 which has a C-
30 and/or N- terminal truncation, wherein the encoded polypeptide has an activity of

the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

5 (e) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

10 (f) a nucleotide sequence of any of (a) - (e) comprising a fragment of at least about 16 nucleotides;

(g) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of any of (a) - (f); and

15 (h) a nucleotide sequence complementary to any of (a) - (e).

4. A vector comprising the nucleic acid molecule of any of Claims 1, 2, or 3.

5. A host cell comprising the vector of Claim 4.

20 6. The host cell of Claim 5 that is a eukaryotic cell.

7. The host cell of Claim 5 that is a prokaryotic cell.

25 8. A process of producing a CHL polypeptide comprising culturing the host cell of Claim 5 under suitable conditions to express the polypeptide, and optionally isolating the polypeptide from the culture.

9. A polypeptide produced by the process of Claim 8.

10. The process of Claim 8, wherein the nucleic acid molecule comprises promoter DNA other than the promoter DNA for the native CHL polypeptide operatively linked to the DNA encoding the CHL polypeptide.

5 11. The isolated nucleic acid molecule according to Claim 2, wherein the percent identity is determined using a computer program selected from the group consisting of GAP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

10 12. A process for determining whether a compound inhibits CHL polypeptide activity or CHL polypeptide production comprising exposing a cell according to any of Claims 5, 6, or 7 to the compound and measuring CHL polypeptide activity or CHL polypeptide production in said cell.

15 13. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12; and

(b) the amino acid sequence encoded by the DNA insert in any of
20 ATCC Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964.

14. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in any of SEQ ID NO: 3, SEQ
25 ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 13, or SEQ ID NO: 14, optionally further comprising an amino-terminal methionine;

(b) an amino acid sequence for an ortholog of any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(c) an amino acid sequence which is at least about 70 percent identical
30 to the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, wherein the polypeptide has an activity of the polypeptide

set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(d) a fragment of the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 comprising at least about 25 amino acid residues, wherein the fragment has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, or is antigenic; and

(e) an amino acid sequence for an allelic variant or splice variant of the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, the amino acid sequence encoded by the DNA insert in any of ATCC Deposit Nos. PTA-961, PTA-962, PTA-963, or PTA-964, or any of (a) - (c).

15. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(b) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(c) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12;

(d) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 which has a C- and/or N- terminal

truncation, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12; and

- (e) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and N-terminal truncation, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12.

10 16. An isolated polypeptide encoded by the nucleic acid molecule of any of Claims 1, 2, or 3, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12.

15 17. The isolated polypeptide according to Claim 14, wherein the percent identity is determined using a computer program selected from the group consisting of GAP, BLASTP, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

20 18. A selective binding agent or fragment thereof which specifically binds the polypeptide of any of Claims 13, 14, or 15.

19. The selective binding agent or fragment thereof of Claim 18 that specifically binds the polypeptide comprising the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12, or a fragment thereof.

20. The selective binding agent of Claim 18 that is an antibody or fragment thereof.

22. The selective binding agent of Claim 18 that is a human antibody
5 or fragment thereof.

10 24. The selective binding agent Claim 18 that is a monoclonal antibody or fragment thereof.

26. The selective binding agent of Claim 18 that is a CDR-grafted antibody or fragment thereof.

27. The selective binding agent of Claim 18 that is an antiidiotypic
20 antibody or fragment thereof.

28. The selective binding agent of Claim 18 that is a variable region fragment.

25 29. The variable region fragment of Claim 28 that is a Fab or a Fab' fragment.

30. A selective binding agent or fragment thereof comprising at least one complementarity determining region with specificity for a polypeptide having the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12.

31. The selective binding agent of Claim 18 that is bound to a detectable label.

5 ~~32.~~ The selective binding agent of Claim 18 that antagonizes CHL polypeptide biological activity.

10 ~~33.~~ A method for treating, preventing, or ameliorating a CHL polypeptide-related disease, condition, or disorder comprising administering to a patient an effective amount of a selective binding agent according to Claim 18.

15 ~~34.~~ A selective binding agent produced by immunizing an animal with a polypeptide comprising an amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 5, SEQ ID NO: 8, or SEQ ID NO: 12.

20 ~~35.~~ A hybridoma which produces a selective binding agent which is capable of binding a polypeptide according to any of Claims 1, 2, or 3.

25 ~~36.~~ A method of detecting or quantitating the amount of CHL polypeptide using the anti-CHL antibody or fragment of Claim 18.

30 ~~37.~~ A composition comprising the polypeptide of any of Claims 13, 14, or 15, and a pharmaceutically acceptable formulation agent.

35 ~~38.~~ The composition of Claim 37, wherein the pharmaceutically acceptable formulation agent is a carrier, adjuvant, solubilizer, stabilizer, or anti-oxidant.

40 ~~39.~~ The composition of Claim 37, wherein the polypeptide comprises the amino acid sequence as set forth in any of SEQ ID NO: 3, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 13, or SEQ ID NO: 14.

40. A polypeptide comprising a derivative of the polypeptide of any of Claims 13, 14, or 15.

5 41. The polypeptide of Claim 40 that is covalently modified with a water-soluble polymer.

42. The polypeptide of Claim 41, wherein the water-soluble polymer is selected from the group consisting of polyethylene glycol, monomethoxy-
10 polyethylene glycol, dextran, cellulose, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide copolymers, polyoxyethylated polyols, and polyvinyl alcohol.

43. A composition comprising a nucleic acid molecule of any of
15 Claims 1, 2, or 3 and a pharmaceutically acceptable formulation agent.

44. The composition of Claim 43, wherein said nucleic acid molecule is contained in a viral vector.

20 45. A viral vector comprising a nucleic acid molecule of any of Claims 1, 2, or 3.

46. A fusion polypeptide comprising the polypeptide of any of Claims 13, 14, or 15 fused to a heterologous amino acid sequence.

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47. The fusion polypeptide of Claim 46, wherein the heterologous amino acid sequence is an IgG constant domain or fragment thereof.

48. A method for treating, preventing, or ameliorating a medical
30 condition comprising administering to a patient the polypeptide of any of Claims

49. The method of Claim 48, wherein the medical condition being
5 treated, prevented, or ameliorated is osteopetrosis or osteoporosis.

(a) determining the presence or amount of expression of the
10 polypeptide of any of Claims 13, 14, or 15, or the polypeptide encoded by the
nucleic acid molecule of any of Claims 1, 2, or 3 in a sample; and

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(a) a membrane suitable for implantation; and

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(b) determining the extent of binding of the CHL polypeptide to the compound.

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56. A process for determining whether a compound inhibits CHL polypeptide activity or CHL polypeptide production comprising exposing a transgenic mammal according to Claim 55 to the compound, and measuring CHL polypeptide activity or CHL polypeptide production in said mammal.